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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/485,640	02/11/2000	HIROYUKI ODAKA	2477US0P	2112

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EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/485,640	ODAKA ET AL.	
	Examiner	Art Unit	
	Shaojia A Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to Applicant's amendment and response filed on October 20, 2003, wherein claim 1 has been amended, and claims 9 and 13 are cancelled, and claim 28 is newly submitted to in place of the cancelled claim 13.

Currently, claims 1 and 28 are pending in this application.

Claims 1 as amended now and new claim 28 are examined on the merits herein.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 as amended now is rejected under 35 U.S.C. 102(b) as being anticipated by Stevenson et al. (of record).

Stevenson et al. discloses that the particular thiazolidinedione, the instant compound, pioglitazone (5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedion) in a dose, i.e., 10 mg/kg (see x-axis for dose in Fig.2 at page 177), is anti-diabetic agent known useful in a composition to be administered to a diabetic patient (e.g. mice) and in treating diabetic complication by lowering both plasma glucose and increasing insulin sensitivity (see Introduction on page 175, and Figure 1 and the last paragraph on page 176), **especially pioglitazone reducing of the elevated Tumor Necrosis Factor -α (TNF-α) mRNA levels by ~50% in mammal** (see 1st paragraph of page 186).

Stevenson teaches that Tumor Necrosis Factor-α (TNF-α) is known to increase insulin insensitivity (see page 185). Thus, TNF-α is tightly associated with diabetic complications. Stevenson's disclosure inherently treats Tumor Necrosis Factor-α mediated diabetic complications in a mammal such as claimed herein since Stevenson's method steps are same as the instant method steps. See *Ex parte Novitski*, 26 USPQ 2d 1389.

Thus, Stevenson et al. anticipates Claim 1.

Applicant's remarks filed on October 20, 2003 with respect to the rejection of claims 1 and 9 made under 35 U.S.C. 102(b) as being anticipated by Stevenson et al. of record stated in the Office Action dated May 19, 2003 have been fully considered but they are not deemed persuasive to render the claimed invention patentable over the prior art as discussed in the set forth 102(b) rejection above.

Applicant arguments that Stevenson et al. do not teach or demonstrate any data to support the treatment of TNF-α mediated diabetic complications with pioglitazone, are not found persuasive. As pointed out above and in the previous Office Action, pioglitazone (5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedion) in a dose, i.e., 10 mg/kg is a known anti-diabetic agent to be administered to a diabetic patient (e.g. mice) in treating diabetic complication by lowering both plasma glucose and increasing insulin sensitivity (see Stevenson et al. Introduction on page 175, and Figure 1 and the last paragraph on page 176), especially pioglitazone reducing of the elevated Tumor Necrosis Factor -α (TNF-α) mRNA levels by ~50% in mammal (see 1st paragraph of page 186). Thus, Stevenson clearly discloses that thiazolidinedione

derivatives herein are reductions in TNF-α. More importantly, Stevenson's method steps are same as the instant method steps.

Further, a chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties Applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not inherently possess the same properties as instantly claimed method administering the same product, pioglitazone. Applicant has not provided any evidence of record to show that the prior art composition of pioglitazone does not exhibit the same properties as instantly claimed.

Therefore, Stevenson et al. anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 28 even though it is not anticipated by Stevenson et al. as applicable to claim 1, is rejected under 35 U.S.C. 103(a) as being unpatentable over the same reference by Stevenson et al. in view of Sohda et al. (WO 96/05186, PTO-892).

The same disclosure of Stevenson et al. has been discussed in the 102(b) rejection above (see supra page 3).

The prior art does not expressly disclose the employment of the particular thiazolidinedione derivative, 5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedion, in a method for treating a Tumor Necrosis Factor-α mediated diabetic complications in a mammal and its effective amount.

Sohda et al. discloses that thiazolidinedione derivatives of formula (I) which has covered and encompassed both pioglitazone (5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedion) and 5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedion, are known antidiabetic agents and also having hypoglycemic acitivity and blood lipid lowering activity, and thus these thiazolidinedione derivatives are useful as medicines (see abstract, page 1 lines 3-7).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular thiazolidinedione derivative, 5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedion, in a method for treating a Tumor Necrosis Factor-α mediated diabetic complications in a mammal, and to determine its effective amounts.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the particular thiazolidinedione derivative, 5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedion, in a method for treating a Tumor Necrosis Factor-α mediated diabetic complications in a mammal, since all thiazolidinedione derivatives of the formula (I) disclosed by Sohda et al. including

pioglitazone and the instant particular compound 5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedion are known antidiabetic agents and also known to be useful in compositions in treating diabetic disease and hyperglycemic diseases and hyperlipidemia. Moreover, hyperglycemic diseases and hyperlipidemia are well known diabetic complications.

Therefore, one of ordinary skill in the art would have reasonably expected that the particular thiazolidinedione derivative, 5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedion would exhibit their known therapeutic effect same as all other derivatives of formula I such as pioglitazone in the method for treating diabetic complications, a Tumor Necrosis Factor-α mediated disease herein, absent evidence to the contrary.

Additionally, pioglitazone which is a structurally substantially similar to 5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedion, is a compound known to possess the properties of reducing of the elevated Tumor Necrosis Factor -α (TNF-α) mRNA levels by ~50% in a diabetic mammal according to Stevenson. The dose of pioglitazone, i.e., 10 mg/kg is also known to be administered to a diabetic patient in treating diabetic complication by lowering both plasma glucose and increasing insulin sensitivity based on the teachings of Stevenson et al. Therefore, the instant compound would be expected to have similar activity as pioglitazone because the compounds having structural similarity would be expected to have same or similar functions and activities. See MPEP 2143.02 and *In re Merck & Co., Inc.*, 800 F.2d, 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further, the determination of another thiazolidinedione derivative to be administered is considered well within the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus, the teachings of Stevenson et al. in view of Sohda et al. have clearly provided the motivation to make the present invention, and the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Applicant's remarks regarding to the rejection of claim 13, filed on October 20, 2003 made under 35 U.S.C. 103(a) of record in the previous Office Action dated May 19, 2003 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art. These remarks are believed to be adequately addressed by the obvious rejection presented above.

Again, Applicant's data shown in the specification at pages 23-28 herein have been fully considered with respect to the nonobviousness and/or unexpected results of the claimed invention over the prior art but are not deemed persuasive for the reasons below. The results on test on the employment of several instant compounds in fatty obese and diabetic rats show expected therapeutic effects as taught and suggested by the cited prior art herein. Therefore, the results herein are clearly expected and not unexpected based on the cited prior art. Expected beneficial results are evidence of obviousness. See MPEP § 716.02(c).

Moreover, it is noted that one of the two tested compounds, Compound 8 is not the instant claimed compound 5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedion in claim 28. Thus, the specification fails to demonstrate any unexpected results of the instant compound in the treatment of TNF-α mediated inflammatory diseases, diabetes and obese. Therefore, the evidence presented in specification herein is not seen to support the nonobviousness of the instant claimed invention over the prior art.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6 and 12 of U.S.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a method of treating diabetes in a mammal comprising administering to such a mammal a therapeutically effective amount of the insulin enhancer selected from the group consisting of pioglitazone (5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedion) and 5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedion. The therapeutically effective amount of these compounds disclosed in patent is 10 mg or 30 mg for example (see Working Example 1-3 at col. 15-16), within the instant claim. The claim of the instant application is drawn to a method for treating TNF-α mediated diabetic complications in a mammal comprising administering the same compounds in the same effective amounts.

Stevenson teaches that Tumor Necrosis Factor-α (TNF-α) is known to increase insulin insensitivity (see page 185), and is thus tightly associated with diabetic complications.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the same active compounds herein in a method for treating TNF-α mediated diabetic complications in a mammal since same active compounds herein are known to be useful in a method of treating diabetes and diabetic complications in a mammal. Therefore, one of ordinary skill in the art would have found it obvious to employ these compounds in a method for treating diabetic complications caused by TNF-α increase in a mammal.

Thus, the instant claims are seen to be obvious over the claims 6 and 12 of U.S. Patent No. 5,965,584 in view of Stevenson et al.

Applicant's remarks regarding to the obviousness-type double patenting rejection, filed on October 20, 2003 of record in the previous Office Action dated May 19, 2003 have been fully considered but are not deemed persuasive. These remarks are believed to be adequately addressed by the obvious rejection presented above.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (703) 305-1008. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
December 29, 2003

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER

1/12/04